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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/551,405 04/17/00 MULLER

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023599 HM22/0507  
MILLEN, WHITE, ZELAND & BRANIGAN, P.C.  
2200 CLARENDON BLVD.  
SUITE 1400  
ARLINGTON VA 22201

EXAMINER

MCKENZIE, T

ART UNIT

PAPER NUMBER

1624

DATE MAILED:

05/07/01

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

## Office Action Summary

Application No.

09/551,405

Applicant(s)

MULLER ET AL.

Examiner

Thomas C McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 19 March 2001.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-8, 10-13 and 16-20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 4 and 18-20 is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-8, 10-13, 16 and 17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

### Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. This action is in response to amendments filed on 3/19/01. There are seventeen pending claims. Claims 1-7 are compound claims. Claims 8, 10-13, and 16-20 are process claims. Applicants have amended claims 4 and 18-20 to be independent claims. This is the second action on the merits. All claims were previously rejected. The application concerns some crystal modifications of calcium N5-methyltetrahydrofolate and processes of preparing them.

#### ***Response to Amendment***

2. Applicants' new abstract is sufficient to overcome the objection made in the previous office action.

#### ***Drawings***

3. Since allowable subject matter has been indicated, applicant is encouraged to submit formal drawings in response to this Office Action. The early submission of formal drawings will permit the Office to review the drawings for acceptability and to resolve any informalities remaining therein before the application is passed to issue. This will avoid possible delays in the issue process.

#### ***Claim Rejections - 35 USC § 112***

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claim 12 is rejected under 35 U.S.C. 112,

first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim has the limitation "crystallization is effected from a suspension." A compound must be dissolved in order for it to be recrystallized. The term recrystallization has no meaning unless the compound being purified by such a process is able to dissolve in the solvent being used for the process. To quote Wiberg "Laboratory Technique in Organic Chemistry" "[r]ecrystallization involves dissolving a substance". This is found in the first sentence in the paragraph labeled "Recrystallization" on page 99.

Applicants have argued that "Applicants intend to define crystallization wherein at no point a clear solution exists" and "the crystalline salts are dissolved within the medium that contains undissolved materials." The claims measure the invention. The U.S. Court of Customs and Patent Appeals wrote *In re Priest*, 199 USPQ 11 "We have consistently held that no "applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim." *In re Prater*, 56 CCPA 1381, 1396, 415 F.2d 1393, 1405, 162 USPQ 541, 551 (1969)."

5. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase “from the resultant heated solution” is indefinite. Are applicants intending crystallization from a hot solution or crystallization at any temperature from a solution that has been heated above 60°C anytime during its history? If they are claiming recrystallization from a hot solution, then how hot must it be? Is 60°C during the crystallization intended or any temperature between 60°C and room temperature?

Applicants state they “intend to define a two step process in claim 8.” “The temperature necessary for crystallization of the transformed product depends upon its concentration in the solution.” Finally, “the solution is cooled after heating ... but the temperature at which crystallization occurs may be above 60°C.” Applicants also point to Examples 7-11 to define their process. Examples 10 and 11 are trituration and not crystallization processes. Examples 7-9 are processes conducted entirely at 90°C. The crystallization mixture is maintained at that temperature as the calcium is added and the crystals form at that temperature. None of this clarifies what Applicants mean by “from the resultant heated solution”. If the three limitations “a two step process”, “temperature necessary for crystallization depends upon on concentration”, and “the solution is cooled after

heating” are critical to Applicants’ process, then claim 8 will be rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Process parameters critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

6. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase “the recrystallization is effected from a suspension” is indefinite. This could mean that a one time the compound being recrystallized was in suspension in the solvent but eventually dissolved. It could mean that the compound being recrystallized was never completely in solution. It could mean that some impurity was never dissolved during the recrystallization process.

Applicants made no argument regarding this rejection.

***Claim Rejections - 35 USC § 102***

7. Claims 1-3, 6-8, and 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Scheib (‘202). Applicants’ first three compound claims have the limitations of a calcium salt, the (6S) absolute configuration, and producing a calcium salt with more than three water molecules of crystallization. Applicants’

claims 6 and 7 are drawn to pentahydrates. Applicants' four process claims have the limitations of heating any salt in water to 85°C and affecting recrystallization. The reference teaches such processes in examples 2-4 in column 2. The N-ethyl-2-aminopyrrolidine salt of N5-methyltetrahydrofolate is recrystallized from water at 85°C. The word "suspended" is used in line 23 of column 2 of the reference, thus anticipating Applicants claim 12. The reference teaches all of these in the first complete paragraph in column 2. Specifically in line 7 of column 2 "X5 H<sub>2</sub>O".

Applicants have argued that the calcium salt of Scheib ('202) is not crystalline. They also point to three passages in this reference to show the non-crystalline nature of the Scheib ('202) material. This is not persuasive. Pauling (General Chemistry) says in the second sentence, final paragraph, page 22 "[m]ost solid substances are crystalline". In the fifth sentence, Pauling (General Chemistry) says "the individual crystal grains of a crystalline substance are small, and the particles of the substance are aggregates of these grains." Scheib ('202) is silent regarding the nature of his salt but Pauling implies, in the absence of contrary evidence, that the Scheib ('202) calcium salt is crystalline. All three passages in Scheib ('202) to which Applicants have pointed concern the pyrrolidine salt not the calcium salt of folic acid, which is the subject of claims 6-8 and 10-13.

Applicants have argued that N-ethyl-2-aminopyrrolidine salt of Scheib ('202) is not crystalline and that the examples cited by Scheib ('202) are conducted at 85°C, not meeting the limitation of claim 10, "above 85°C". This is not persuasive. In line 1, column 2, Scheib ('202) is quite explicit, "the crystals". While the examples of this reference are conducted at 85°C, lines 47-48, column 1 of the reference says "[h]eating the reaction mixture to 40-90 ...".

Applicants have argued that Scheib ('202) does not teach a pentahydrate. This is not persuasive because the phrase "X5 H<sub>2</sub>O", cited above, is art recognized to mean pentahydrate.

8. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Muller ('655). Applicants' first three compound claims have the limitations of a calcium salt, the (6S) absolute configuration, and producing a calcium salt with more than three water molecules of crystallization. Applicants' claims 6 and 7 are drawn to pentahydrates. The reference teaches all of these in lines 34-58 of column 7. Specifically Muller ('655) teaches in line 42 "the dihydrate" and in line 50 "pentahydrate". Applicants' claim 5 is drawn to a dihydrate crystalline salt. Muller ('655) teaches in line 42 of column 7, "the dihydrate".

Applicants argue that the material of Muller ('655) is not crystalline. They also say "the structure is amorphous since the pH value of about 4". This is not

persuasive. Muller ('655) is explicit about the nature of his calcium salt "left to crystallize" and "recrystallized" in lines 51 and 52, column 7. If the pH of the solution is critical to Applicants' process, then claims 1-3 and 5-7 will be rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Process parameters critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

9. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Marazza ('611). Applicants' two compound claims have the limitations of either the (6S) or the (6R) absolute configuration, and producing a salt with at least one water molecule of crystallization. The references teaches all of these in lines spanning lines 50 of column 9 to line 6 of column 11. The reference teaches the cyclohexylammonium salt and the elemental analysis reported in line 36 and 67 of column 10 makes clear this salt is a dihydrate.

Applicants argue that the salt of Marazza ('611) is not crystalline. This is not persuasive. In line 12, column 10, the references teaches "treated with seed crystals". In line 16, column 10, it says "the obtained crystalline solid". In line 46, column 10, "treated with authentic seed crystals". In lines 48-49, "crystalline solid". In lines 18-19, column 11, "crystalline solid".

10. Claims 1-3, 6-8, 10, 11, and 13, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Vecchi ('850). Applicants' first three compound claims have the limitations of a calcium salt, the (6S) absolute configuration, and producing a calcium salt with more than three water molecules of crystallization. Applicants' claims 6 and 7 are drawn to pentahydrates. The reference teaches all of these in lines 5-13 of column 4. The reference teaches a crystalline compound with a water content of 15.27%, which meets the limitation of more than three molecules of water of crystallization. Applicants' six process claims have the limitations of heating a calcium salt in water to above 85°C and effecting recrystallization. The reference teaches such processes in line 5 of column 4 "[i]t can be recrystallized from boiling water". Water boils at 100°C, thus anticipating all of applicants claim limitations.

Applicants argue that the salt of Vecchi ('850) is not crystalline and that the processes of crystallization and recrystallization refer to a mechanical process of separating a liquid from a solid but do not have any implications as to the form of the solid product obtained. This is highly unpersuasive. In addition to the repeated usage of the words crystallization and recrystallization by the reference, in lines 7-8 of column 4, Vecchi ('850) characterizes his calcium salt as "[a]spect: white brown crystalline powder". Hawley (The Condensed Chemical Dictionary) defines

crystallization as “[t]he phenomenon of crystal formation”. The prefix re in re crystallization, implies that crystal formation is repeated a second time. Loewenthal (A Guide for the Perplexed Organic Experimentalist, 2nd Ed), in the last five lines of page 145 makes clear that the result of both processes is a crystalline compound.

Applicants have argued that Vecchi ('850) does not teach a pentahydrate. This is not persuasive because the moisture content reported by this reference corresponds to a pentahydrate.

11. Claims 1, 3, 6, and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Gennari ('500). Applicants' first two compound claims have the limitations of a calcium salt with more than three water molecules of crystallization and racemic N5-methyltetrahydrofolate. Claims 6 and 7 are drawn to pentahydrates. The reference teaches all of these in Example 7 in lines 1-28 of column 7. The reference teaches a “crystalline salt” in line 24 and “pentahydrate” in lines 26-27, which meets the limitation of applicants' claims.

Applicants argue that the salt of Gennari ('500) is not crystalline because it is obtained by precipitation. They further argue that the reference's use of an inert gas and a stabilizer is evidence that his product is not crystalline. This is not persuasive. Hawley (The Condensed Chemical Dictionary) does not have a listing

for precipitation but defines precipitate as “[s]mall particles that have settled out of a liquid ...”. The first example of a precipitate offer by Hawley (The Condensed Chemical Dictionary), barium sulfate, is crystalline. Pauling (General Chemistry), cited above, makes clear that these small particles consist of aggregates of individual crystal grains. The Examiner is unsure of the relevance of inert gas and a stabilizer to the nature of the product formed.

*Allowable Subject Matter*

12. Claims 4 and 18-20 are allowed. The following is a statement of reasons for the indication of allowable subject matter: the prior art does not teach the trihydrate salt of Type I. Thus, the process of converting this salt into the other crystal forms must be novel as well.

*Conclusion*

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any


extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Conclusion***

14. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.



**Mukund Shah  
Supervisory Patent Examiner  
Art Unit 1624**

TCMcK   
May 5, 2001